

REMARKS

Status of the Claims

Claims 1-15 and 17-31 are pending in the application.

Claims 9, 14 and 18-31 have been withdrawn from consideration pursuant to 37 C.F.R. §1.142(b).

Claims 1-8, 10-13, 15 and 17 are currently under consideration with entry of this Response.

Summary

Claims 1-15 and 17-31 are pending in the application, and claims 1-8, 10-13, 15 and 17 were examined in the Office Action dated 10 November 2008. Applicants note with appreciation that the rejection of claims 1-8, 10-13, 15 and 17 under 35 U.S.C. §112, first paragraph, has been withdrawn. However, the following claim rejections have either been maintained or are newly raised by the Office: (a) claims 1-8, 10-13, 15 and 17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 30-37 of copending Application No. 11/183,477 (“the ‘477 Application”); (b) claims 1-8, 10-13, 15 and 17 stand rejected under 35 U.S.C. §112, first paragraph, on the basis of written description; and (c) claims 1-8, 10-13, 15 and 17 stand rejected under 35 U.S.C. §103(a) as unpatentable over International Publication No. WO 00/45790 to Berry et al. (“Berry”) and U.S. Patent Publication No. US 2003/0180364 to Chen et al. (“Chen”) in combination alone or further in view of Kasraian et al. (1999) Pharm. Dev. and Tech 4(4):475-480 (“Kasraian”) and U.S. Patent Publication No. US 2002/0064536 to Hunt (“Hunt”). Applicants respectfully traverse all pending claim rejections for the following reasons.

The Obvious-Type Double Patenting Rejection

Claims 1-8, 10-13, 15 and 17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 30-37 of the ‘477 Application. Applicants respectfully traverse the provisional rejection on the basis that

the alleged conflicting claims have not in fact been granted. Applicants further request that the provisional rejection continue to be held in abeyance until allowable subject matter has been determined in the present application.

The Rejection under 35 U.S.C. §112, first paragraph

Claims 1-8, 10-13, 15 and 17 stand rejected under 35 U.S.C. §112, first paragraph, on the basis of written description. In particular, the Office has objected to the claim limitation “wherein the polymer was treated with methionine in an amount sufficient to reduce vehicle peroxide values below 5 ppm” on the basis that applicants have “only” taught a method of removal of peroxides from PVP using a 1% L-methionine solution and then diafiltration to remove residual L-methionine.” Office Action at page 5. The Office asserts “this disclosure does not teach how much methionine solution is used” and then concludes “therefore, the specification does not provide written description for ‘in an amount sufficient’” and further that “the disclosure does not teach if other polymers can also be treated with methionine to achieve peroxide values below 5 ppm.” Office Action at page 5. Applicants respectfully traverse the rejection.

The first paragraph of 35 U.S.C. 112 requires that the “specification shall contain a written description of the invention.” This requirement is separate and distinct from the enablement requirement. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991). See also *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920-23, 69 USPQ2d 1886, 1890-93 (Fed. Cir. 2004) (discussing history and purpose of the written description requirement). The analysis of whether the specification complies with the written description is conducted from the standpoint of one of skill in the art at the time the application was filed (see, e.g., *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art. Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be

described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

At paragraph [0045] of applicants' specification as originally filed, applicants provide working examples of how to remove peroxides from a polymer vehicle. In particular, applicants disclose a simple washing technique for removal of peroxides, where a 1% L-methionine solution is used to wash the polymer excipient, and then a diafiltration process is used to remove excess L-methionine. Applicants further disclose a standard laboratory technique to measure peroxide levels in the washed polymer. The field of the invention is pharmaceutical formulation chemistries, and the level of skill in the art is generally high, with practitioners typically having post-graduate degrees such as Masters, Ph.D., MD or PharmD degrees. Such ordinarily skilled persons understand what applicants intend when they instruct how to make a 1% solution of L-methionine. These same skilled persons understand what applicants intend when they instruct that the polymer preparation should be washed using a 1% solution of L-methionine. The skilled person understands that the L-methionine amino acid acts as an oxidative sink (scavenger for oxidizing compounds) and the methionine residue is selected on the basis that it is subject to oxidation. The skilled person understands that use of such an oxidative sink is not dependent on the polymer species, and the same person further understands that one should remove excess L-methionine residues from the pharmaceutical product, and finally the skilled person understands what applicants intend when they instruct that one should conduct a standard assay to determine how many ppm peroxides are present in the polymer preparation after a washing step. All of this sort of information is both well known and clearly available to the skilled person, and does not need to be described in any more detail than what is provided by applicants' specification.

For all of the foregoing reasons, then, the rejection of claims 1-8, 10-13, 15 and 17 under 35 U.S.C. §112, first paragraph, is improper. Applicants have provided a sufficient written description of the recited invention. When applicants' specification and claims are properly assessed by the ordinarily skilled artisan, it is clear that applicants have complied with their written description obligation. In addition, even though enablement is not properly an issue under Section 112, first paragraph, the enablement

issues raised by the Office are likewise improper (it is readily apparent that any polymer can be treated as taught by applicants, and it is readily apparent to the skilled person regarding how to carry out applicants' recited methionine washing treatment).

The Rejection under 35 U.S.C. §103

Claims 1-8, 10-13, 15 and 17 stand rejected under 35 U.S.C. §103(a) as unpatentable over Berry and Chen, in combination alone or further in view of Kasraian and Hunt. In particular, the Office asserts that the combination of Berry and Chen would make it “*prima facie* obvious ... to form a stable, nonaqueous composition by combining the interferon, polyvinylpyrrolidone and solvent of Berry with the omega-interferon, polyvinylpyrrolidone and benzyl alcohol of Chen in order to arrive at the claimed invention, with a reasonable expectation of success.” Office Action at page 8. The Office goes on to assert “[w]ith respect to the polymer being treated with methionine ... to reduce vehicle peroxide values below 5 ppm, Berry does not specifically teach the treatment of the polymer with methionine to reduce the peroxide values of the formulation. However, Berry does teach that peroxides ... adversely affect protein stability [and] would be toxic ... [t]herefore, one skilled in the art would assume that the peroxide values of the formulations [of] Berry and Chen would also be less than 5 ppm” Office Action at page 8. The Office goes on to rely on Kasraian and Hunt to teach presence of peroxides in polymers, and use of amino acids such as methionine as an oxidative sink (Office Action at page 9), and then concludes “it would have been obvious ... to treat a polymer such as polyvinylpyrrolidone with methionine in order to reduce peroxide values below 5 ppm, thus arriving at the claimed invention.” Office Action at page 10. Applicants respectfully traverse the rejection for the following reasons.

When considering the patentability of claims under Section 103, the following tenets of patent law must be adhered to: (a) the claimed invention must be considered as a whole; (b) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (c) the references must be viewed with the benefit of impermissible hindsight vision afforded by the claimed invention; and

(c) reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

The Office's proposed combination of Berry and Chen fails to establish a *prima facie* showing of obviousness. In order to arrive at applicants' recited invention, the Office has spotted a discussion of peroxides in lipid vehicles from the Berry background discussion, and has ignored the plain teaching provided by that reference and failed to consider the Berry disclosure as a whole. The Office has pointed to the Berry disclosure at page 4, lines 22-24. These lines are the last lines of the paragraph that begins at line 11 of page 4, where Berry note that "[d]ispersing powdered proteins or peptides in lipid vehicles to yield parenteral sustained release formulations has been investigated." Berry's paragraph goes on to note that "although theoretically these vehicles [lipid vehicles] might preclude solution denaturation and protect the drug from aqueous chemical degradation, the vehicles themselves are unstable at higher temperatures [and] storage of liquid vegetable oils at body temperature results in the formation of reactive species such as free fatty acids and peroxides." The paragraph then concludes with the lines that the Office has spotted, where Berry notes the adverse affects of peroxides. As one reads the rest of the Berry disclosure, it is apparent that Berry offers as a solution to, *inter alia*, the above-noted problems with lipid vehicles, certain polymer formulations can be used instead. Thus, Berry highlights a number of problems with prior art vehicles (such as problems with peroxides in lipid vehicles) and teaches, as a solution to this problem, that their polymer compositions should be used instead.

Accordingly, when Berry is considered as a whole (as required under Section 103), it is clear that Berry believed that the use of their polymer formulations would avoid peroxide problems – i.e., Berry believed that use of their polymer formulations would avoid peroxide problems as seen with prior lipid vehicle formulations. This is in stark contrast to the assertion by the Office that it was obvious to treat a polymer vehicle, using applicants' recited methionine washing procedure to arrive at applicants' critical maximum peroxide value of 5 ppm or less. Berry therefore completely fails to teach or suggest the desirability and thus the obviousness of applicants' recited formulations that contain a polymer vehicle that has been treated in a specific manner to arrive at a

peroxide value of 5 ppm or less. In fact, Berry actually teaches away from applicants' recited invention. The Chen reference likewise fails to teach or suggest applicants' recited invention. Accordingly, the Office's proposed combination of Berry and Chen – when those references are considered as a whole for what they fairly teach the skilled person – fails to establish a *prima facie* showing of obviousness. Reconsideration and withdrawal of the rejection of claims 1-8, 10-13, 15 and 17 under 35 U.S.C. §103(a) over Berry and Chen in combination alone is thus earnestly solicited.

With regard to the Office's proposed combination of the primary references to Berry and Chen in further view of Kasraian and Hunt, applicants respectfully submit that this combination is also improper and fails to establish a *prima facie* showing of obviousness of applicants' recited invention when that invention is considered as a whole as required under Section 103. More particularly, the failure of the primary references (Berry and Chen) to teach or suggest the desirability, and thus the obviousness of applicants' recited formulations has been established herein above. Berry actually teaches away from the invention and Chen fails to provide the missing disclosure. In light of this failure in the primary references, the secondary references (Kasraian and Hunt) also fail to fill-in the missing teachings.

Kasraian, when read as a whole for what it teaches the skilled person, merely identified peroxide content in a PVP excipient, and then taught that one should add an antioxidant to their pharmaceutical formulation (and thus not remove the peroxide source). See Kasraian, beginning of the paragraph in the second column of page 476. There is simply nothing in Kasraian that leads back to the primary references, and nothing in the primary references that would lead to Kasraian. Accordingly, the only way to combine Kasraian with Berry and Chen is through an impermissible hindsight reconstruction of applicants' recited invention. In addition, even if one combined Kasraian with Berry and Chen, one does not arrive at applicants' recited invention, where the polymer vehicle is washed with methionine to arrive at applicants' critical peroxide value of 5 ppm or less.

Hunt, when read as a whole for what it teaches the skilled person, merely teaches use of oxidative sinks. There is simply nothing in Hunt that leads back to the primary

references, and nothing in the primary references that would lead to Hunt. Accordingly, the only way to combine Hunt with Berry and Chen is through an impermissible hindsight reconstruction of applicants' recited invention. In addition, even if one combined Hunt with Berry and Chen, one does not arrive at applicants' recited invention, where the polymer vehicle is washed with methionine to arrive at applicants' critical peroxide value of 5 ppm or less.

Accordingly, the Office's proposed combination of Berry and Chen in further view of Kasraian and Hunt fails to teach or suggest applicants' invention. The Office failed to consider the actual teaching of Berry and thus misapplied the discussion from Berry regarding peroxides. Without this improper reading of Berry, there is simply nothing to connect the primary references to Berry and Chen with the secondary references to Kasraian and Hunt. In addition, even if one does combine those references, using an impermissible hindsight reconstruction of applicants' claimed invention, one still does not arrive at applicants' whole invention. Without this necessary showing in the proposed combination, there simply cannot have been a reasonable expectation for success for arriving at applicants' invention – one cannot have a reasonable expectation for success for something which was both unknown and non-obvious.

Accordingly, contrary to the Office's assertions, the proposed combination of Berry and Chen in further view of Kasraian and Hunt fails to establish a showing of *prima facie* obviousness. Reconsideration and withdrawal of the rejection of claims 1-8, 10-13, 15 and 17 under 35 U.S.C. §103(a) is thus earnestly solicited.

CONCLUSION

Applicants submit that the pending claims define an invention that is both novel and nonobvious over the cited art, and thus all claims are in condition for allowance. Acknowledgement of this by the Office in the form of an early allowance is thus respectfully requested. In addition, if the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, applicants invite the Examiner to contact the undersigned at (408) 777-4915.

The appropriate fee is either attached or authorized. If the Commissioner determines that an additional fee is necessary, the Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. **50-1953**.

Respectfully submitted,



Thomas P. McCracken
Registration No. 38,548

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For and on behalf of
DURECT CORPORATION
10240 Bubb Road
Cupertino, CA 95014
Phone: (408) 777-4915
Fax: (408) 777-3577